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Report

# Traces of Experience in the Lateral Entorhinal Cortex

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## Summary

**A growing body of evidence suggests that memories are stored in the hippocampus by integrating spatial information from specialized cell types in the medial entorhinal cortex (MEC) with nonspatial information from cells in the lateral entorhinal cortex (LEC) [1–5]. LEC neurons show little spatial modulation when rats run in empty open-field environments [6, 7] but fire in the vicinity of discrete objects [7], suggesting that they provide information about the specific content of the spatial environment. It is unclear, however, whether firing at objects is elicited purely by stimulus properties, in a sensory-like manner, or whether any higher-order property, such as the history of experience, is also relevant. To address this question, we recorded from LEC neurons in an open field where objects were present on a subset of the trials. Whereas some neurons fired at the objects, other cells developed specific firing at places where objects had been located on previous trials, providing a readout of past experience in the environment. The latter cells generally did not respond to the object when it was present, suggesting that object cells and object-trace cells are independent cell classes. These findings identify LEC as a component of the hippocampal-cortical circuit for object-place memory.**

## Results

The entorhinal cortex is the main interface between the hippocampus and the neocortex. Considering the pivotal role of hippocampal-neocortical interaction in the formation of long-term memory [8–10], we asked whether memory of specific experience is detectable in the activity of principal cells in the entorhinal cortex. We focused on the lateral entorhinal cortex (LEC) because of its strong bidirectional connections with the anterior cingulate cortex [11, 12], a cortical area thought to orchestrate retrieval of remote memories that depend on the hippocampus for their initial formation [13–18]. Recordings were made from deep and superficial LEC layers (Figure 1A; see also Figure S1 available online) while rats ran a session of three trials consisting of an object-free trial, a trial with an object (Figure 1B), and another object-free trial. Object shape and location were kept constant. Once a responsive cell was identified, typically after 20 or more training sessions, the animal was tested with different shapes of objects, different object locations, and different environments. Responses to objects were quantified by comparing mean firing rate in a defined area around the object against the mean rate outside this location. For each cell, the deviation from the mean activity outside the object location was expressed as a z score (the number of standard deviations above the expected activity).

We first confirmed that the LEC contains cells that respond specifically at the location of the object [7]. A large number of cells exhibited weak responses at and around the object when it was present (Figure 1C, middle). A total of 127 out of 432 cells had z scores above 2 (29.4%; Figure 1D). A total of 61 cells had z scores above 5 (14.1%; Figure 1D). The mean firing rate at the object location was 3.34 Hz for cells with $z > 2$ and 4.32 Hz for cells with $z > 5$. The mean rate outside the object location was 1.88 and 2.19 Hz, respectively. The cells showed minimal firing at the object location on trials without the object (only three cells, or 4.9%, of the cells with z scores above 5 continued to pass the $z = 5$ threshold; mean rate for these cells was 4.30 Hz; Figure 1E). The number of object cells with fields at the former object location on the post-object trial ($z > 2$: 6/127 cells, or 4.7%; $z > 5$: 3/61 cells, or 4.9%) was not larger than in the general cell population ($z > 2$: 67/432 cells, or 15.5%; $z > 5$: 22/432 cells, or 5.1%).

On the post-object trial, an additional but smaller proportion of cells—"object-trace cells"—had responses corresponding to where the object had been on the preceding trial (67 cells, or 15.5%, with z scores above 2; 22 cells, or 5.1%, with z scores above 5; Figure 1C bottom; Figures 1E and S1). Their mean firing rates at the former object location were 2.89 Hz ($z > 2$) and 4.49 Hz ($z > 5$); mean outside firing rates were 1.60 Hz and 1.58 Hz, respectively. These cells discharged only minimally when the object was present (2.29 Hz for $z > 5$; object versus post-object mean rates: $t[42] = 2.0$, $p < 0.05$, paired t test). The number of object-trace cells with fields at the object on the object trial was not larger than expected by chance in the general population (for $z > 2$: 10/67 cells, or 14.9%, compared to 127/432 cells, or 29.4%, in the overall population; for $z > 5$: 3/22 cells, or 13.6%, compared to 61/432 cells, or 14.1%, in the overall population; Figure 1D), suggesting that object cells and object-trace cells are functionally distinct cell groups.

Object and trace responses in the form of decreases in activity were observed as well, but the magnitude of such responses was smaller than for increases in activity (58 cells, or 13.4%, with z scores below −2, and no cells with z scores below −5, for object trials; 56 cells, or 12.9%, with z scores below −2, and one cell, or 0.02%, with z score below −5, for post-object trials). On object trials, the mean firing rate of cells with z scores $< -2$ at the object location was 1.11 Hz; mean firing rate outside the object location was 1.99 Hz. On post-object trials, the mean firing rate at the former object location was 1.01 Hz ($z < -2$); mean firing rate outside the object location was 1.94 Hz.

To further investigate the properties of object-trace cells, we selected a subset of 22 cells with strong trace properties, using a conservative threshold of $z > 5$. We were able to record from six cells of this subset over multiple sessions and across as much as 17 days after the initial standard object session. In these sessions, trace responses at the standard location persisted ($z > 5$), despite the fact that the object was no longer

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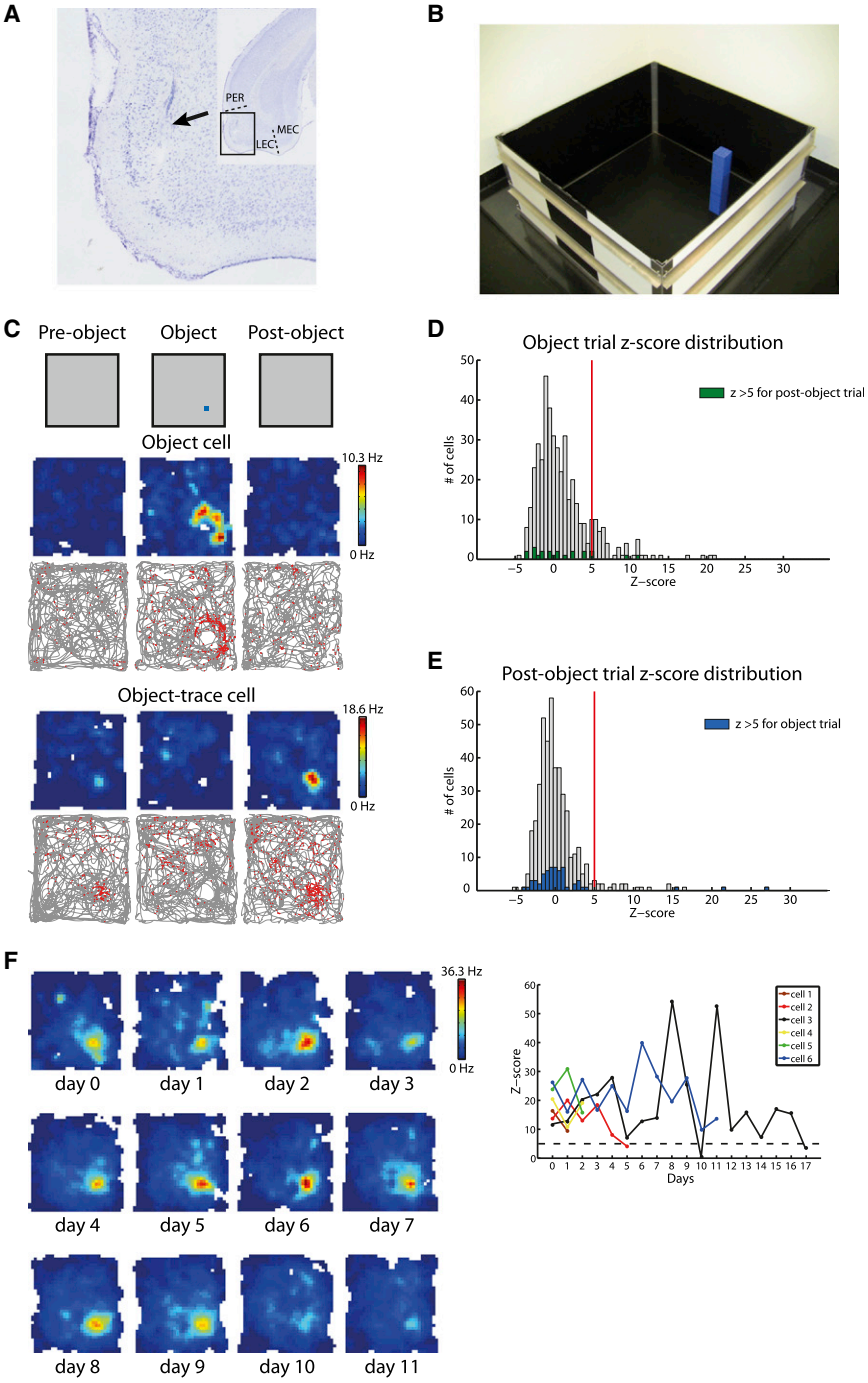


Figure 1. Trace Responses in Lateral Entorhinal Cortex

(A) Coronal brain section showing representative electrode location in lateral entorhinal cortex. Arrow indicates recording position. Inset shows low-magnification section of the same section. PER, perirhinal cortex; LEC, lateral entorhinal cortex; MEC, medial entorhinal cortex. See also Figure S1.

(B) Recording box with familiar object at familiar location (standard task).

(C) Top: cartoon of standard experiment. The three trials (pre-object, object, post-object) were separated by approximately 1 min. Middle: example cell with object response. Bottom: example cell with object-trace response. Path plots with spikes overlaid are shown below corresponding rate maps. Rate maps are color coded (scale bar indicates minimum and maximum rates). The trace field in the bottom row is present even before the object trial, reflecting tests with identical object locations on prior days.

(D) Distribution of z scores on the object trial for all cells recorded in the standard experiment. Red line indicates z = 5 criterion.

(E) Distribution of z scores on the post-object trial for all cells in the standard experiment. Red line indicates z = 5 criterion. For (D) and (E), object responses of object-trace cells are shown in green and object-trace responses of object cells in blue. Note that cells with large z scores on one trial type do not generally have large scores on the other, suggesting that object cells and object-trace cells are independent populations.

(F) Left: example cell with persistent trace field at the standard location of the familiar object (trial with highest z score of the day is shown). The object was presented for the last time at the standard location on day 0. Right: highest z score for former object location versus rest of environment for each day, including all trace cells recorded for more than 1 day (only tests with familiar object location).

See also Figure S1.

present at this location (Figures 1F and S1B). The persistence of trace activity over many days of extinction rules out the possibility that the firing on the post-object probe trial was merely a mismatch response to the absence of object stimuli.

Following the completion of standard sessions, identified trace cells were probed by varying the location and shape of the object. We first examined whether different object locations could be encoded by a single trace cell (six trace cells). The familiar object was moved sequentially to six places on the floor of the recording box (Figure 2A). The trace cells acquired and maintained strong firing fields at each new object location after the object was removed (Figures 2B–2D and S2A; mean trace cell z score for all object locations immediately post-object: 11.78 ± 0.52). The emergence of trace fields at the novel locations was generally accompanied by a lack of response to the present object (mean trace cell z score across all locations for present object location: 0.56 ± 0.70, t[5] = 0.81, p = 0.46). A response to the current object was seen only in one trace cell in one location (Figure 2F), suggesting again that object-trace cells are functionally distinct from object cells. Additionally, although trace fields were observed at all six novel locations in the immediate post-object trial, these newly formed trace fields began to fade by 1 hr and largely disappeared by 3–4 hr after the object test (Figures 2C–2E and S2B; mean trace cell z score immediately post-object: 9.30 ± 2.03; 1 hr post-object: 6.36 ± 1.89; 3–4 hr post-object: 4.58 ± 0.84; immediate versus 3–4 hr; t[10] = 2.69, p < 0.05). The disappearance of fields at novel locations coincided with a reemergence of the trace field at the familiar location (Figure 2E; mean trace cell z score for familiar location versus all other locations was −0.53 ± 1.33

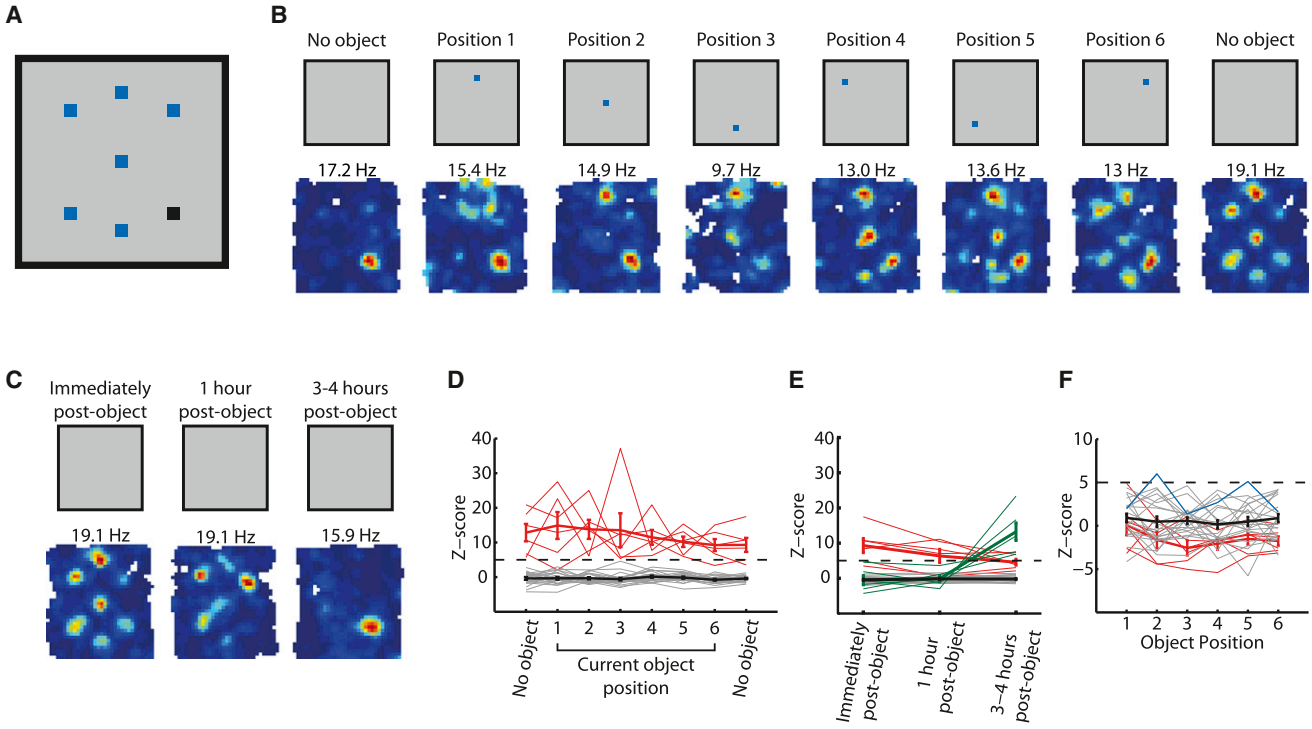


Figure 2. Trace Cell Responses When the Object Is Moved to a New Location

(A) Cartoon showing new object locations (blue) as well as the former standard location (black).

(B) Top row: cartoon showing object position on individual trials. Bottom row: example cell with trace fields that follow the movement of the object. In each location, trace fields emerge one trial after the presentation of the object. Note that trace fields accumulate across trials.

(C) Decay of trace fields at novel object locations and return of single dominating trace field at the overtrained object location.

(D–F) z scores for all cells recorded in the multiple-location experiment.

(D) Scores compare activity at all former object locations with activity in the rest of the environment (n = 6 trace cells, in red; 21 nontrace cells, in gray). Trace response during initial no-object trial is due to prior sessions with the familiar object. Average number of locations evoking a significant response ($z > 5$) was six—one cell responded to four of six locations, all others responded to all six locations. In the immediate post-object sessions of this experiment, the average number of locations with significant responses ($z > 5$) was three.

(E) Same as (D), but for decay trials starting from immediately post-object to 3–4 hr post-object. Green lines indicate trace cell z scores for the familiar location versus the rest of the environment (identical to z score calculation for standard session). Because there are fields outside of the familiar location, and because in some cases the firing at the familiar location was reduced once other locations were introduced, the z score is low on the first post-object trials.

(F) Scores compare trace-cell activity at the current object location with activity in the rest of the environment. A high z score would reflect a direct response to the object, as seen with object cells. Blue line indicates nontrace cell with object responses, bold lines indicate means for trace (red) and nontrace (black) cells. SEMs are indicated. Peak firing rates are indicated above each rate map.

See also Figure S2.

immediately after the last novel location, compared to 13.26 ± 2.51 at 3–4 hr later, $p < 0.001$).

Having presented only a highly familiar object up until this point, we next introduced objects of different size and shape (five trace cells). Experiments were identical to standard sessions, except that during the object trial, we used a novel object, placed at a different location. Trace responses were again observed on the post-object trial in all trace cells tested (Figures 3A and S3; mean trace cell z score: 11.38 ± 1.24, compared to mean nontrace cell z score: 0.77 ± 0.36, $p < 0.0001$). Only one trace cell and one nontrace cell responded significantly during the object trial (trace cell: $z = 6.48$, mean trace cell z score during object session: 2.13 ± 1.88; nontrace cell: $z = 13.33$, mean nontrace cell z score during object session: 1.55 ± 0.58) (Figures S3B and S3C). Similar to trace responses evoked by the familiar object at novel locations, trace fields evoked by novel objects disappeared by 3–4 hr (Figure 3A; mean trace cell z score 3–4 hr post-object: 3.50 ± 1.14, compared to 11.38 ± 1.24 on the immediate post-object trial; $t[8] = 4.68$, $p < 0.01$).

If object-trace cells serve a function in memory for individual experiences, they should distinguish between spatial contexts. To test whether trace responses are context-selective, we observed the cells while the animals ran in a novel environment. Trace responses were not transferred to the novel environment (Figures 3B and S3D; mean spatial correlation across environments, A versus B: 0.18 ± 0.12; mean spatial correlation between initial and final trial in the familiar environment, A versus A′: 0.60 ± 0.05, $p < 0.01$). This was not due to an insufficient amount of time for the trace representation to stabilize, because the mean spatial correlation comparing the first 10 min in the novel environment to the second 10 min was not different from the mean spatial correlation comparing the first familiar environment trial to the second familiar environment trial (0.40 ± 0.12 versus 0.60 ± 0.05, $t[10] = 1.50$, $p = 0.16$).

When the familiar object was introduced in the novel environment, trace responses were observed in all five cells (Figures 3C and S3E; mean trace cell z score during

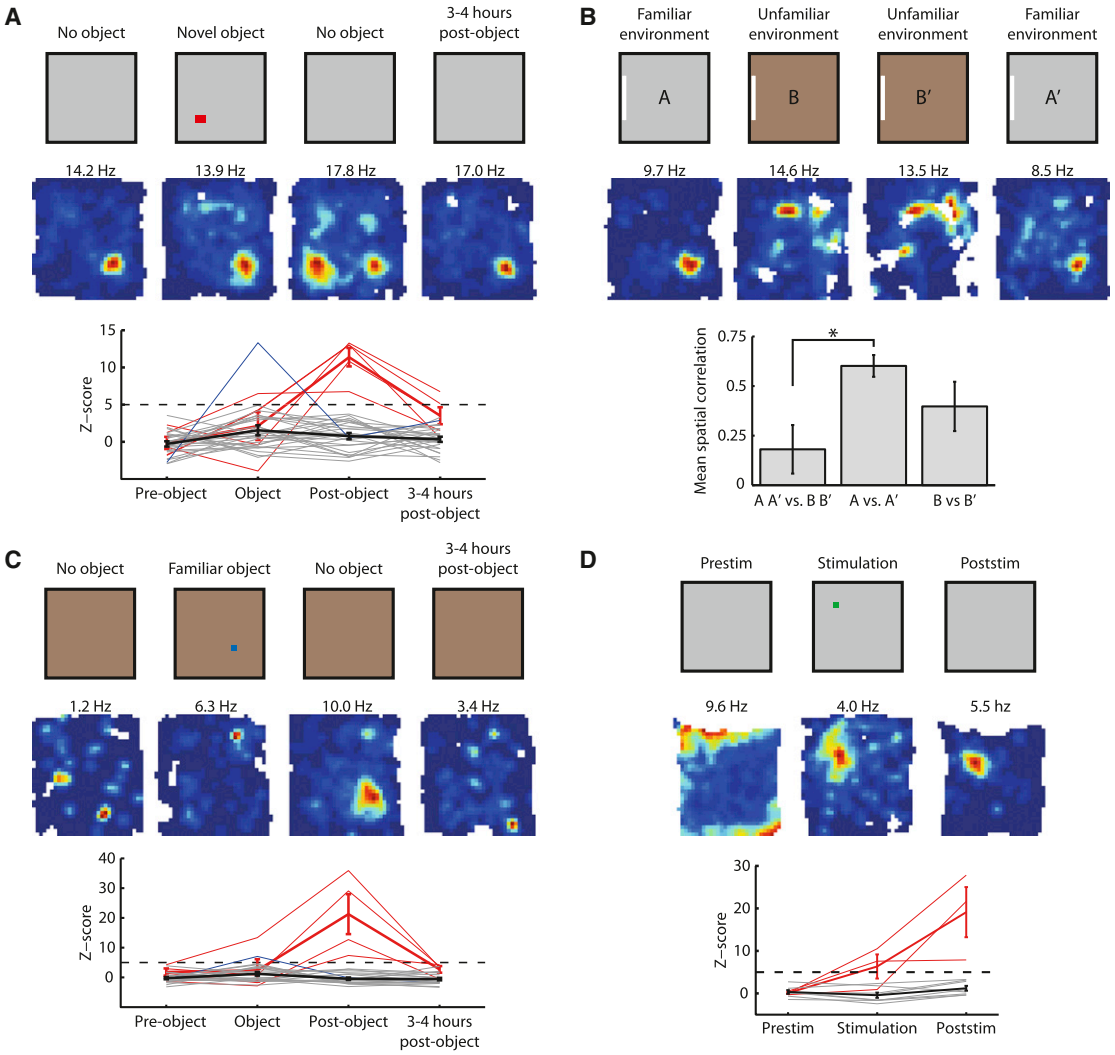


Figure 3. Trace Cell Responses after Replacement of Object or Change of Environment

(A) Top: cartoon showing new object in new location. Middle: example cell with trace field in response to novel object. Bottom: z scores for all cells recorded in the novel-object experiment (n = 5 trace, 27 nontrace cells; red, trace cells; blue, object cell; gray, all other cells).

(B) Top: cartoon showing test of transfer to new environment. Cue card and wall color, as well as environment shape, remained constant across environments. Cue card locations are indicated by white stripes. Middle: example cell with context-dependent trace field. Bottom: spatial correlations between environments (n = 6 trace cells; means ± SEM).

(C) Top: cartoon showing familiar object in new environment. Middle: example cell with trace field on post-object trial. Bottom: z scores for all cells in novel environment (n = 4 trace, 19 nontrace cells).

(D) Top: cartoon showing medial forebrain bundle (MFB) stimulation in a confined location. MFB stimulation caused animals to spend nearly twice as much time in the stimulation zone compared to time spent around the physical objects (~142 s in stimulation zone, compared to ~43 s around physical objects). Middle: example cell with trace field corresponding to stimulation location. Bottom: z scores for trace cells and simultaneously recorded nontrace cells in the stimulation experiment (n = 3 trace, 8 nontrace cells). For all z score plots, red lines indicate trace cells, gray lines indicate nontrace cells, blue lines indicate nontrace cells with object responses, and bold lines indicate means for trace (red) and nontrace (black) cells. SEMs are indicated. Peak firing rates are indicated above each rate map.

See also Figure S3.

post-object trial: 21.26 ± 6.72, compared to mean nontrace cell z score: −0.45 ± 0.42, t[22] = 7.37, p < 0.00001), but as with all other unfamiliar stimuli that we tested, responses faded away by 3–4 hr (mean trace cell z score 3–4 hr post-object: 2.69 ± 1.10, compared to 21.26 ± 6.72 on the immediate post-object trial, t[6] = 2.73, p < 0.05). In the novel environment, only one trace cell responded to the object when it was present (z = 13.37, mean trace cell z score during object trial: 2.37 ± 3.74), indicating that the function of trace cells remains constant across environments.

Finally, we asked whether trace responses were confined to physical objects or instead spanned a wider range of stimuli. A separate group of animals was trained on standard sessions in which the familiar object was replaced with microstimulation of the medial forebrain bundle (MFB) [19, 20]. Microstimulation was given when the animal entered a set reward zone. Across 51 cells, three exhibited trace responses at the reward zone on the poststimulation trial (Figures 3D and S3G; mean trace cell z score: 19.12 ± 5.90, compared to mean nontrace cell z score for simultaneously recorded

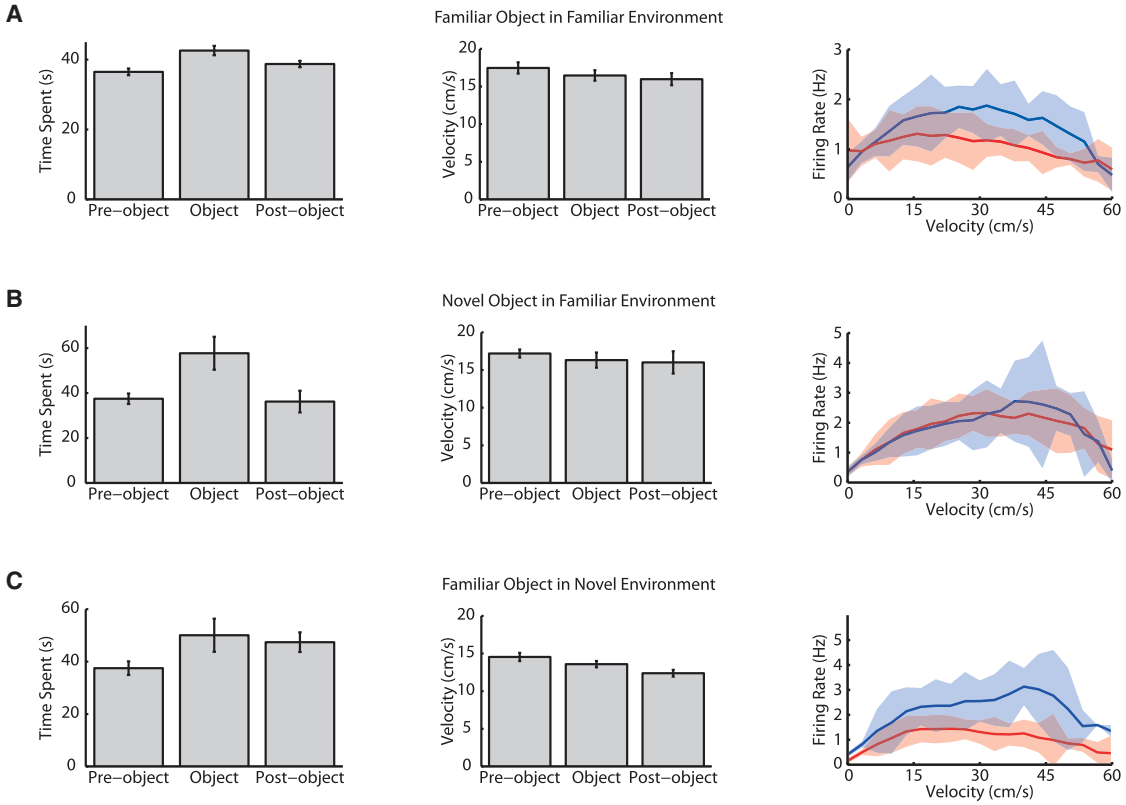


Figure 4. Trace Responses Are Not Caused by Changes in Behavior

Left: time spent in object location (mean ± SEM). Middle: velocity at object location (mean ± SEM). Right: firing rate of trace cells across a range of velocities for pre-object (red) and post-object (blue) trials (shadowed areas indicate SEM; distribution smoothed by a moving average filter with a span of 5).

(A) Familiar object in familiar environment (n = 22 trace cells).

(B) Novel object in familiar environment (n = 5 trace cells).

(C) Familiar object in novel environment (n = 4 trace cells).

cells: 0.21 ± 0.57, t[9] = 5.27, p < 0.001). In two cells demonstrating trace responses to MFB stimulation, significant responses were also observed during stimulation (z scores of 7.58 and 10.51), although this could reflect direct polysynaptic effects.

Across all experiments, including the MFB stimulation experiments, animals invariably changed their behavior in the presence of the object (Figures 3D and 4). However, trace responses were not merely due to changes in behavior. The rats ran at slightly lower mean velocities during the post-object trials, but the object-trace cells fired across a broad range of velocities, and there was no difference in the firing rate of these cells between pre- and post-object trials for any velocity.

## Discussion

We have identified a population of LEC cells that respond specifically at locations where the animal has previously encountered an object. This population of object-trace cells is distinct from other cell types in the temporal lobe. First, they differ from the object-responsive cells previously described in the LEC itself [7]. Few trace cells fired in the presence of the object, and few object cells fired after removal of the object, suggesting that object-trace cells and object cells are independent and largely nonoverlapping populations. The trace cells are reminiscent of object-responsive LEC cells that continue to fire after removal of the object [21, 22] but differ in that the trace cells lack object selectivity and fire specifically when previously experienced objects are absent. Second, the generalized firing of object-trace cells over a variety of object shapes and object locations also makes these cells different from cells with specific paired-associate responses in the inferior temporal cortex of monkeys [23, 24]. Third, trace cells differ from "misplace" or mismatch cells described in early studies of hippocampal spatial firing [25–27]. Such cells were reported to fire when animals detect a new object or find that a familiar object has been removed; however, the firing of these neurons was confined to the initial seconds after the detection of the mismatch. Trace cells, in contrast, always fired for at least one full trial and, with sufficient experience, for weeks without any decline in the firing rate. The persistent firing of the trace cells also contrasts with the short-lasting response to nonspatial stimuli observed in a variety of cell types in the hippocampal system [28, 29]. Finally, object and object-trace cells differ from hippocampal place cells in that place cells remain stable or remap when an objects is moved and do not, like entorhinal trace cells, systematically follow the object [30]. Moreover, place cells primarily reflect the present environment, unlike trace cells, which exclusively reflect past object locations. Collectively, our observations suggest that trace cells are unique in that they respond specifically under conditions where animals would retrieve object-location associations from recent or remote memory.

Trace activity in the LEC may influence information storage in the hippocampus. The findings suggest that LEC neurons provide two types of input—information about the presence of discrete objects at particular spatial locations, and information about locations that contained such objects in the past. The LEC code is thus spatial in that it expresses information about location but lacks the metric of the grid and direction codes in the medial entorhinal cortex [2, 31, 32]. Trace activity in LEC may be functionally linked to history-dependent firing in the hippocampus, such as the persistence of firing patterns in place cells after all relevant spatial cues have been removed [33–38] or the retrospective firing on a spatial alternation task [39, 40]. Trace cells may also correlate with conjunctive object-place coding [41–43] as well as firing at locations paired with reward [44–46] in the hippocampus. However, whether trace cells serve as input to hippocampal cells with such firing patterns or rather reflect output from them remains to be established. The presence of trace activity in both deep and superficial cell layers leaves both possibilities open. Additional work is required to determine the exact function of trace cells and their interaction with memory representations in the hippocampus.

The properties of trace cells in the LEC are remarkably similar to those of a functional cell type recently reported in the anterior cingulate cortex (ACC). This cell type responds specifically to where in a spatial environment an object was located during previous visits to that environment [17, 18]. The presence of ACC cells whose firing is influenced by experiences from as much as a month earlier is consistent with gene activation studies showing increased activity in ACC during retrieval of remote spatial or contextual memory as well as impaired retrieval of such memories following temporary inactivation of the ACC [13–16]. Taken together, these studies suggest that the ACC operates as a central node in the brain's network for memory retrieval. The present findings point to LEC as a possible interface between early-stage memory networks in the hippocampus and late-stage memory networks coordinated through the ACC. How these networks work together remains to be determined. The hippocampus and the ACC have virtually no direct connections but are strongly linked through the LEC. The rostral and intermediate regions of the dorsal ACC, which contain the object-trace cells of that region [17, 18], have strong reciprocal connections with the superficial and deep layers of the dorsolateral parts of LEC [11, 12]. The relations to the ACC establish object-trace cells of the LEC as a candidate for interfacing the hippocampus with cortical networks for retrieval of object-space relationships from long-term memory.

## Experimental Procedures

Single unit activity was recorded from tetrodes in LEC of eight Long-Evans rats (0.1 mm anterior of lambda, 6.0–7.0 mm lateral to midline, 4.0 mm below dura, 4–8 degrees outward in the coronal plane). Animals were trained to forage a 1 × 1 × 0.5 $m^3$ black box with a white cue card and, on some trials, an object. Objects were composed of Lego bricks.

Responses to the object were quantified on object trials and post-object trials using *z* scores, calculated as $z = (X - \overline{X})/(s/\sqrt{n})$, with $X$ the mean firing rate in a 22.5 × 22.5 cm area containing and surrounding the object, $\overline{X}$ the mean rate outside the object location, $s$ the standard deviation of the mean rate outside the object location, and $n$ the number of bins defining the object location [18]. Mean activity outside the object location was calculated from a matching number of bins randomly selected from the outside area.

Experiments were performed in accordance with the Norwegian Animal Welfare Act and the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes.

## Supplemental Information

Supplemental Information includes three figures and Supplemental Experimental Procedures and can be found with this article online at http://dx.doi.org/10.1016/j.cub.2013.01.036.

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